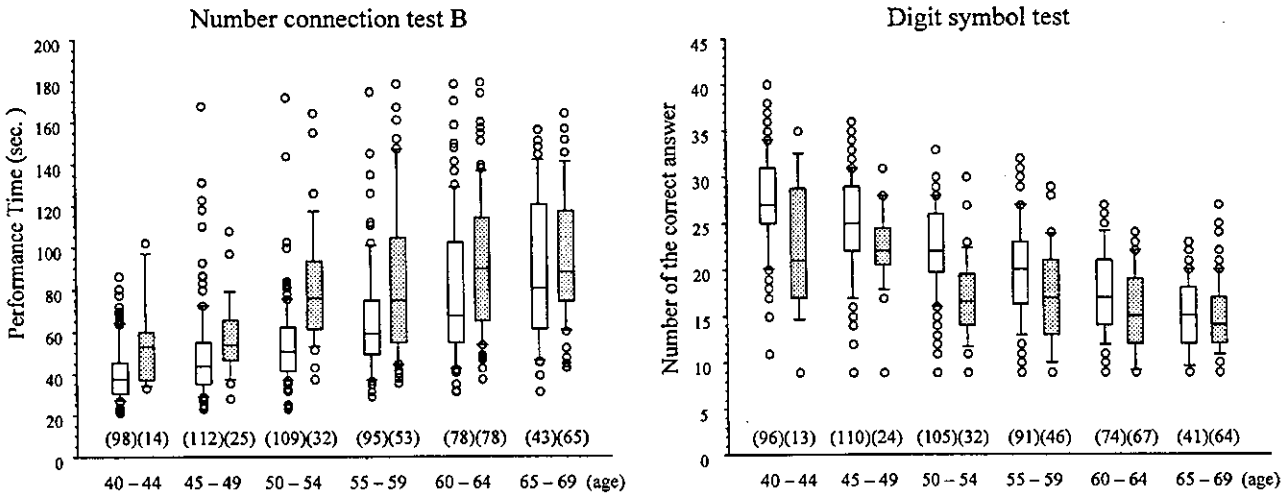


Fig. 2. Results of number connection test B and digit symbol test in healthy subjects and cirrhotic patients are indicated with horizontal bars. The vertical bars indicate the range and the horizontal boundaries of boxes represent the first and third quartiles: (□) healthy subjects; (▨) cirrhotic patients (*n*).

sults and their standard deviations become increasingly variable with age (data not shown), test data were compiled at 5-year age intervals and shown by the quartile range (box and whisker plots). Results of NCT-B and DST are shown in Fig. 2 as typical results obtained. Test results obtained from both healthy subjects and cirrhotic patients showed clear age-related changes, with the test time increasing and the number of correct answers decreasing with age. The test time increased and the number of correct answers decreased in cirrhotic patients compared to healthy subjects regardless of age up to 65. Among those aged 65 or older, however, there were no significant differences between healthy subjects and cirrhotic patients. Results of all tests showed similar effects of aging as well as the differences between healthy subjects and cirrhotic patients.

Data were missing from 11 healthy subjects (2%) for DST and 1 healthy volunteer (0.2%) for all of the 7 other tests, while among hepatic cirrhosis patients, 7 (2.4%) gave no data for NCT-A, 25 (8.6%) for NCT-B, 19 (6.5%) for FPT, 46 (15.8%) for DST, 6 (2%) for BDT, and 11 (3.8%) for RT-A, B and C. DST data were missing from the largest number of subjects in both the healthy volunteer and hepatic cirrhosis patient groups.

Cut-off values were determined based on the upper and lower 10th, 20th and 30th percentiles, which are regarded as outliers in healthy subjects, and were set at the upper and lower 10th percentile due to great variability because of the effects of aging on standard deviations. The percentage of liver cirrhosis patients who were regarded as giving abnormal values based on the 10th/90th percentile cut-off value in healthy subjects and the test results obtained at 5-year intervals ranged between 9 and 47% for NCT-B and 21.0% overall and between 2 and 44% for DST and 18.7% overall. The percentage of liver cirrhosis patients who gave abnormal values in the eight tests varied according to the age bracket and ranged between 10 and 25% (Table 2). Of the 292 cirrhotic patients, 170 (58.2%) showed deviations from the 10th percentile cut-off value with respect to at least 1 test item.

## 5. Discussion

We developed a computer-aided quantitative neuropsychological test system in order to facilitate the diagnosis of SHE associated with liver cirrhosis.

Results obtained with this test system showed apparent differences between healthy subjects and liver cirrhosis patients without clinical hepatic encephalopathy (grade 0 or 1). Both healthy subjects and liver cirrhosis patients showed increases in the test time and decreases in the number of correct answers with age, and it was evident that the results of the neuropsychological tests need to be analyzed at 5-year age intervals. The results of the present study thus indicated that major shortfalls of the this test method are the great variability of the test results in both healthy subjects and liver cirrhosis patients and increases in the test time with age even in healthy subjects. The test method seemed to be able to differentiate healthy subjects from liver cirrhosis patients and attribute the difference to subclinical encephalopathy if they are younger than 65. In older patients, however, discrimination seemed to be impossible and the test method seemed to have its own limitation.

Although the tests were not repeated in the same patients, it was thought that they could be properly conducted in liver cirrhosis patients as well as in healthy subjects because data were missing from only a few patients.

Among various factors with possible effects on the test results, blood ammonia levels affected the test results, but the severity of hepatic dysfunction did not. Test results obtained in the present study were not significantly different

Table 2
Estimated abnormal rate of cut-off value (10th/90th percentile; healthy subjects) and standard value by NP-test (the data represents medians, with interquartile ranges)

| Age (years) | Healthy subjects | | | | | Cirrhotic patients | | | Estimated abnormal | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | 25th | Median | 75th | 90th | 25th | Median | 75th | % | *n* |
| NCT-A | | | | | | | | | | |
| 40–44 | 98 | 20.7 | 24.8 | 29.3 | 36.2 | 25.2 | 31.4 | 42.7 | 35.7 | 5/14 |
| 45–49 | 112 | 23.2 | 27.3 | 34.4 | 41.7 | 26.7 | 31.2 | 34.6 | 3.9 | 1/26 |
| 50–54 | 109 | 25.8 | 31.4 | 35.6 | 41.4 | 33.6 | 40.7 | 51.3 | 42.4 | 14/33 |
| 55–59 | 98 | 28.4 | 33.4 | 42.5 | 51.0 | 33.2 | 38.9 | 45.5 | 16.7 | 9/54 |
| 60–64 | 78 | 32.6 | 37.5 | 44.3 | 55.8 | 36.1 | 46.0 | 52.5 | 17.3 | 14/81 |
| 65–69 | 45 | 33.7 | 45.1 | 54.4 | 62.1 | 36.6 | 45.0 | 56.8 | 14.3 | 11/77 |
| Total | 540 | | | | | | | | 18.9 | 54/285 |
| NCT-B | | | | | | | | | | |
| 40–44 | 98 | 30.4 | 37.5 | 45.3 | 64.1 | 36.8 | 53.2 | 59.8 | 21.4 | 3/14 |
| 45–49 | 112 | 35.3 | 43.5 | 54.7 | 72.7 | 46.6 | 54.0 | 65.7 | 16.0 | 4/25 |
| 50–54 | 109 | 41.4 | 50.4 | 62.4 | 76.1 | 61.2 | 75.9 | 93.7 | 46.9 | 15/32 |
| 55–59 | 95 | 49.3 | 59.2 | 74.8 | 101.0 | 54.7 | 74.9 | 104.8 | 28.3 | 15/53 |
| 60–64 | 78 | 55.0 | 67.4 | 102.5 | 129.1 | 65.1 | 90.0 | 114.5 | 16.7 | 13/78 |
| 65–69 | 43 | 61.4 | 80.5 | 121.1 | 142.4 | 74.7 | 88.7 | 117.5 | 9.2 | 6/65 |
| Total | 535 | | | | | | | | 21.0 | 56/267 |
| FPT | | | | | | | | | | |
| 40–44 | 98 | 1.3 | 1.6 | 2.1 | 2.4 | 1.6 | 2.7 | 3.5 | 57.1 | 8/14 |
| 45–49 | 112 | 1.4 | 1.8 | 2.2 | 3.0 | 1.6 | 2.0 | 2.6 | 19.2 | 5/26 |
| 50–54 | 108 | 1.4 | 1.9 | 2.4 | 3.7 | 1.8 | 2.3 | 2.8 | 15.2 | 5/33 |
| 55–59 | 96 | 1.5 | 1.9 | 2.7 | 3.7 | 1.9 | 2.2 | 2.8 | 11.5 | 6/52 |
| 60–64 | 77 | 1.7 | 2.2 | 2.9 | 3.8 | 1.9 | 2.7 | 3.4 | 22.1 | 17/77 |
| 65–69 | 41 | 1.8 | 2.5 | 3.8 | 6.2 | 2.4 | 3.1 | 4.6 | 9.9 | 7/71 |
| Total | 532 | | | | | | | | 17.6 | 48/273 |
| DST | | | | | | | | | | |
| 40–44 | 96 | 20.0 | 25.0 | 27.0 | 31.0 | 17.0 | 21.0 | 28.8 | 30.8 | 4/13 |
| 45–49 | 110 | 17.0 | 22.0 | 25.0 | 29.0 | 20.5 | 22.0 | 24.5 | 4.2 | 1/24 |
| 50–54 | 105 | 16.0 | 19.8 | 22.0 | 26.0 | 14.0 | 16.5 | 19.5 | 43.8 | 14/32 |
| 55–59 | 91 | 13.0 | 16.3 | 20.0 | 23.0 | 13.0 | 17.0 | 21.0 | 21.7 | 10/46 |
| 60–64 | 74 | 11.9 | 14.0 | 17.0 | 21.0 | 12.0 | 15.0 | 19.0 | 23.9 | 16/67 |
| 65–69 | 41 | 9.6 | 12.0 | 15.0 | 18.0 | 12.0 | 14.0 | 17.0 | 1.6 | 1/64 |
| Total | 517 | | | | | | | | 18.7 | 46/246 |
| BDT | | | | | | | | | | |
| 40–44 | 98 | 9.1 | 10.6 | 12.4 | 14.9 | 10.9 | 16.0 | 17.9 | 57.1 | 8/14 |
| 45–49 | 112 | 10.3 | 12.9 | 16.0 | 18.6 | 12.3 | 14.4 | 17.5 | 22.2 | 6/27 |
| 50–54 | 109 | 11.3 | 13.9 | 16.7 | 19.7 | 12.5 | 15.6 | 20.0 | 27.3 | 9/33 |
| 55–59 | 99 | 11.9 | 14.6 | 20.7 | 27.1 | 13.4 | 17.8 | 23.5 | 11.1 | 6/54 |
| 60–64 | 79 | 13.9 | 17.5 | 21.5 | 25.8 | 15.2 | 20.6 | 27.3 | 25.6 | 21/82 |
| 65–69 | 45 | 15.7 | 20.3 | 24.8 | [28.5 | 19.5 | 23.9 | 28.8 | 27.5 | 22/80 |
| Total | 542 | | | | | | | | 24.8 | 72/290 |
| RTT-A | | | | | | | | | | |
| 40–44 | 98 | 0.300 | 0.331 | 0.373 | 0.427 | 0.312 | 0.379 | 0.436 | 25.0 | 3/12 |
| 45–49 | 111 | 0.302 | 0.353 | 0.402 | 0.487 | 0.316 | 0.410 | 0.479 | 22.2 | 6/27 |
| 50–54 | 109 | 0.328 | 0.372 | 0.434 | 0.521 | 0.332 | 0.394 | 0.529 | 30.0 | 9/30 |
| 55–59 | 99 | 0.331 | 0.367 | 0.471 | 0.623 | 0.361 | 0.408 | 0.508 | 11.1 | 6/54 |
| 60–64 | 79 | 0.348 | 0.412 | 0.502 | 0.639 | 0.381 | 0.497 | 0.625 | 21.3 | 17/80 |
| 65–69 | 45 | 0.348 | 0.417 | 0.635 | 0.875 | 0.435 | 0.565 | 0.718 | 10.3 | 8/78 |
| Total | 541 | | | | | | | | 17.4 | 49/281 |
| RTT-B | | | | | | | | | | |
| 40–44 | 98 | 0.331 | 0.363 | 0.393 | 0.432 | 0.352 | 0.394 | 0.440 | 30.8 | 4/13 |
| 45–49 | 112 | 0.333 | 0.365 | 0.402 | 0.474 | 0.361 | 0.389 | 0.410 | 18.5 | 5/27 |
| 50–54 | 109 | 0.344 | 0.375 | 0.420 | 0.465 | 0.352 | 0.385 | 0.442 | 23.3 | 7/30 |
| 55–59 | 99 | 0.349 | 0.385 | 0.448 | 0.556 | 0.356 | 0.392 | 0.436 | 9.3 | 5/54 |
| 60–64 | 79 | 0.363 | 0.394 | 0.445 | 0.568 | 0.367 | 0.437 | 0.520 | 19.0 | 15/79 |

Table 2 (*Continued*)

| Age (years) | Healthy subjects | | | | | Cirrhotic patients | | | Estimated abnormal | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | 25th | Median | 75th | 90th | 25th | Median | 75th | % | *n* |
| 65–69 | 45 | 0.379 | 0.420 | 0.561 | 0.812 | 0.416 | 0.486 | 0.586 | 5.1 | 4/78 |
| Total | 542 | | | | | | | | 14.2 | 40/281 |
| RTT-C | | | | | | | | | | |
| 40–44 | 98 | 0.352 | 0.392 | 0.445 | 0.508 | 0.386 | 0.445 | 0.599 | 30.8 | 4/13 |
| 45–49 | 112 | 0.386 | 0.427 | 0.490 | 0.627 | 0.373 | 0.419 | 0.466 | 14.8 | 4/27 |
| 50–54 | 109 | 0.385 | 0.424 | 0.499 | 0.647 | 0.382 | 0.436 | 0.519 | 3.3 | 1/30 |
| 55–59 | 98 | 0.388 | 0.422 | 0.513 | 0.700 | 0.385 | 0.444 | 0.529 | 11.1 | 6/54 |
| 60–64 | 79 | 0.398 | 0.468 | 0.572 | 0.670 | 0.397 | 0.455 | 0.601 | 16.5 | 13/79 |
| 65–69 | 44 | 0.395 | 0.444 | 0.590 | 0.903 | 0.445 | 0.518 | 0.632 | 1.3 | 1/78 |
| Total | 540 | | | | | | | | 10.3 | 29/281 |

between alcoholic and non-alcoholic cirrhosis patients. Aging also showed profound effects on the test results. Weissenborn et al. [14] also reported that aging has significant effects on the NCT-A and NCT-B results. Neuropsychological tests have been reported to show learning effects or effects of increasing familiarity with the tests as they are repeated [6,20]. However, we noted no such effects with our system because it was designed so that only a short practice is conducted before the main tests. The level of education is also expected to affect the test results, but this effect was thought to be minimal on our test system because our test system is relatively simple and more than 90% of the population in Japan receives education for at least 12 years. Some of the liver cirrhosis patients enrolled in our study were taking drugs for hyperammonemia, but these drugs had no effects on the test results and abnormalities could be detected by each test.

Abnormal values for the tests included in our test system were determined based on the results obtained from healthy adult volunteers. The cut-off values were set at the 10th/90th percentiles, which are statistical outliers in healthy subjects, so that abnormal values were not overestimated. The incidence of abnormalities determined in liver cirrhosis based on these cut-off values was about 25% for each test, and 58.2% of the 292 liver cirrhosis patients showed deviations from the 10th/90th percentile cut-off values for at least 1 test. These percentages are lower than the 30–84% prevalence of SHE reported in liver cirrhosis patients [1–14]. Because our data were obtained from a large number of subjects in a multicenter clinical trial, however, the 10th/90th percentile cut-off values determined by us are expected to provide a simple method to screen SHE patients from liver cirrhosis patients. SHE is suspected if the results of any of the eight tests included in our test system are abnormal, but further studies are needed to determine if the diagnosis of SHE should be made only when two or more tests give abnormal values.

In general, SHE is diagnosed based on the results of multiple tests designed to assess performance cognition. Our test system also assesses multiple performance cognition functions (psychomotor function, attention, memory, and special cognition function) based on the results of eight tests. At present, there is no method in which test results are scored to make a diagnosis of SHE based on overall assessment of the test results. We were also unable to draw any definite conclusion from the scoring of the test results. Our results showed, however, that many liver cirrhosis patients who show abnormality in one test also show abnormality in other tests. In the future, it will be necessary to weight each test before scoring the abnormalities and making an overall assessment of the test results.

Recently, 11 types of neuropsychological tests conducted by Weissenborn et al. [14] and the CFF test [16] showed that low-grade HE could be diagnosed with great sensitivity and specificity, but their SHE extraction rate was similar to that obtained by us, and we do not believe that the diagnostic sensitivity can be enhanced by increasing the number of tests conducted.

Because the test results are affected by a number of factors such as the subject's physical condition, fatigue, sleeping time, experience operating computers, ocular disease, and testing environment, it is recommended that these factors be eliminated as much as possible when using our test system.

At present, there is no standard diagnostic method or criteria for SHE in Japan. The computer-aided quantitative neuropsychological test system developed by us converted two- or three-dimensional tests using paper and blocks into two-dimensional tests that can be conducted using a touch panel so that SHE can be easily diagnosed in daily clinical practice. Because the main objective of the present study was to computerize the tests commonly conducted to diagnose SHE, the test system developed by us was not compared to the conventional tests using paper and blocks. Further studies are needed to determine if our test system is superior to the conventional test methods.

Further prospective studies are also needed to determine, using the test system developed by us, the percentage of patients in whom SHE progresses to clinical hepatic encephalopathy by conventional coma grade, and determine the effects of SHE on quality of life by SF-36 (Short form 36) and the relationship between SHE and etiology of liver cirrhosis.

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# Functional network in the prefrontal cortex during episodic memory retrieval

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**A recent consistent finding in neuroimaging studies of human memory is that the prefrontal cortex (PFC) is activated during episodic memory retrieval. To date, however, there has been no direct evidence to explain how activity in the right and left PFC and in the anterior and posterior PFC are functionally interconnected. The goal of the present study was to obtain such evidence by event-related functional magnetic resonance imaging (MRI) and the functional connectivity method. Subjects were first asked to try to remember a series of associate-word lists outside the MRI scanner in preparation for a later recognition test. In the MRI scanning phase, they were asked to make recognition judgments in regard to old words, semantically related lure words, and unrelated new words. The analysis of functional connectivity revealed that the posterior PFC in each hemisphere had strong functional interconnections with the contralateral posterior PFC, whereas the anterior PFC in each hemisphere had only weak functional interconnections with the contralateral anterior PFC. No strong functional interconnections were found between the anterior and posterior PFC in either hemisphere. These findings support the hypothesis of an associative contribution of the bilateral posterior PFC to episodic memory retrieval and a dissociative contribution of the bilateral anterior PFC.**


*Keywords:* Prefrontal cortex; Functional connectivity; Episodic memory; False recognition

## Introduction

A consistent finding in recent functional neuroimaging studies of human memory is that the lateral prefrontal cortex (PFC) is activated during episodic memory retrieval (Buckner and Wheeler, 2001; Cabeza and Nyberg, 2000; Fletcher and Henson, 2001; Rugg and Wilding, 2000). Some of the studies have shown the right and left PFC to have separate roles during episodic retrieval processes (for reviews, see Buckner and Wheeler, 2001; Fletcher and Henson, 2001; Ramnani and Owen, 2004), and several of them have indicated that the function of the right PFC is within the context of strategic attitudes during retrieval (Düzel et al., 1999; Kapur et al., 1995; Nyberg et al., 1995; Rugg and Wilding, 2000; Rugg et al., 2000; Schacter et al., 1996a), of products of retrieval (McDermott et al., 2000; Rugg et al., 1998; Wagner et al., 1998), and of evaluational monitoring processes during or after retrieval (Allan et al., 2000; Henson et al., 1999b; MacLeod et al., 1998; Rugg et al., 1999). The function of the left PFC, on the other hand, has been characterized as being strategic retrieval of source information (Rugg, 1999; Ranganath and Paller, 1999; Ranganath et al., 2000) and semantic processing (Poldrack et al., 1999). Although some of these findings are based on the laterality data of broader PFC activations that include the anterior and posterior regions, many of these findings are based on the data showing activations in the anterior regions of the PFC. Some comprehensive hypotheses that focus on the functional interrelation between the PFC regions have also been proposed. One hypothesis states that the right PFC subserves more heuristic (automatic) judgments based on easily assessed qualities, such as familiarity or perceptual detail, whereas the left PFC subserves more systematic judgments requiring more deliberative decisions (Johnson and Raye, 1998; Nolde et al., 1998a,b; Ranganath et al., 2000; Raye et al., 2000).

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Another hypothesis states that the right PFC is more involved in monitoring and verification, whereas the left PFC is more involved in the production of semantically guided information (Cabeza et al., 2003).

Other studies have shown the anterior ventrolateral and posterior dorsolateral PFC to have separate roles, and several hypotheses have been proposed to explain the functional interrelation between the anterior and posterior PFC. One hypothesis, based on the results of previous studies on cognitive control, states that the posterior PFC supports response selection, which implements context-dependent biasing or dynamic filtering (Banich et al., 2000; MacDonald et al., 2000; Miller and Cohen, 2001), or refreshing, which is required for reactivation of representations that were recently active but have subsequently begun to decay (Johnson et al., 2002, 2003; Raye et al., 2002), whereas the anterior PFC supports managing subgoals and integrating representations during the course of ongoing processing (Badre and Wagner, 2004). Another hypothesis based on the results of studies on working memory states that the posterior PFC subserves the monitoring and manipulation of the representations held in material-independent working memory, whereas the anterior PFC subserves the maintenance and evaluation of representations held in material-specific working memory (Wagner, 1999). Yet, another hypothesis states that the posterior PFC is involved when externally generated information is being evaluated, whereas the anterior PFC becomes recruited when internally generated information needs to be evaluated (Christoff and Gabrieli, 2000).

Although these hypotheses describing the functional interrelations between the right and left PFC and between the anterior and posterior PFC have to some extent been supported by previous studies, there has been no direct evidence showing whether the functions of the four PFC regions (right anterior, left anterior, right posterior, and left posterior PFC) are completely dissociate or partly dissociate during episodic memory retrieval. Since the similarity and diversity have been postulated to exist among the processing components of episodic memory retrieval, the functions of four PFC regions may be partly dissociate. The functional connectivity method may be useful in answering these questions. It has often been used to identify the temporal coherence among neuronal activity in spatially distinct brain regions by applying imaging data obtained by fMRI and positron emission tomography (PET) (Büchel and Friston, 1998; Büchel et al., 1999; Friston, 1994; Friston et al., 1995c).

A previous study that focused on functional interconnections within the PFC network during memory retrieval showed that the right PFC regions (BA 9, 10, and 47) were positively associated during recall (Cabeza et al., 1997), and other studies have provided evidence of a functional differentiation of the right anterior PFC (BA 10) and right posterior PFC (BA 45/47) (McIntosh, 1999; McIntosh et al., 1997). Brain areas whose activity during recognition was found to be positively correlated with activity in the right anterior PFC included widespread areas of the PFC and inferior temporal cortex bilaterally (Grady et al., 2001). Although these findings regarding prefrontal interconnections are very helpful, the functional interconnections among the four PFC regions during episodic memory retrieval remain unclear.

In the present study, we used functional magnetic resonance imaging (fMRI) and the functional connectivity method to reveal the interconnections among the four PFC regions during episodic memory retrieval. To accomplish our purpose, we should use a task that requires subjects to employ all four PFC regions. We therefore used a revised version of the typical false recognition task referred to as the DRM paradigm originally created by Deese (1959) and Roediger and McDermott (1995). In previous neuroimaging studies, which used the original DRM paradigm, the bilateral anterior and posterior PFC regions and the medial temporal regions were activated during retrieval (Cabeza et al., 2001; Schacter et al., 1996b, 1997). To ensure activation in all four PFC regions, we made the task more difficult by requiring subjects to make a recognition judgment in regard to words presented in pairs. This modification increases the possibility of involving all four PFC regions during performance of the task, because maintaining responses to paired words requires more complicated retrieval processes and higher working memory load. Evidence of strong functional connectivity between the right and left PFC would suggest that the two hemispheres function in collaboration. Weak or no connectivity between the right and left PFC would suggest that the two hemispheres function independently and would support their having separate roles. Moreover, if different functional connectivity patterns were found between the two hemispheres in the anterior and posterior PFC and weak or no connectivity between the anterior and posterior PFC, it would suggest that the functions of four PFC regions are partly dissociate.

Based on the results of the previous neuroimaging findings described above, we hypothesized an associative right–left functional interconnection in the posterior PFC (areas $Y \geq 50$ in the middle frontal gyrus) and a dissociative right–left functional interconnection in the anterior PFC (areas $Y < 50$ in the middle frontal gyrus), and the hypothesis predicted that different right–left connectivity patterns would be found in the anterior and posterior PFC. To test it, we first compared activation patterns associated with three types of responses (hit, false alarm, and correct rejection), then conducted the time-course analyses of MR signals to identify the temporal characteristics of the patterns in specific PFC regions, and finally, examined the functional interconnections among those regions by means of a connectivity analysis.

## Materials and methods

### *Subjects*

Thirteen healthy subjects (ten males and three females; average age 27.4 years; average years of education 16.3) were paid to participate in this study. Handedness was assessed by the Edinburgh Handedness Survey (Oldfield, 1971), and all subjects were right-handed. The fMRI experiments were conducted under a protocol approved by the Institutional Ethics Committee of the National Institute of Radiological Sciences of Japan. All of the subjects gave written informed consent prior to participation in the experiment.

### *Materials*

The material consisted of 24 theme sets of 15 semantic associate words (a total of 360 words) and was largely based on the study lists used by Roediger and McDermott (1995). We modified some of the words because they would have been inappropriate for Japanese subjects. In preparation for the fMRI experiment, 10 healthy subjects were recruited and requested to rate the degree of association of the words from their theme words on a five-point scale. We then averaged each of the association

values to obtain a new association order for each theme set. We used 18 of the 24 theme sets in the study phase of the experiment, and the other six sets were used as unrelated new word sets in the test (MRI scanning) phase.

*Procedure*

The overall procedure used in the present study was similar to that of the typical false recognition task (DRM paradigm), except that we presented the test words in pairs to make the task more difficult (Roediger and McDermott, 1995; Schacter et al., 1996b, 1997).

First, each subject was individually asked to try to remember 18 theme sets of 14 semantic associate words (e.g., *butter*, *toast*, *sandwich*, *eat*, ...) in preparation for a later memory test in the scanner. The theme word (e.g., *breakfast*) and the third strongest associate (e.g., *jam*) from the 18 theme sets were not presented during the study phase and were used as related lures in the test phase. Subjects listened to a total of 252 words at a rate of 1700 ms per word, and none of the words was presented more than once. The words were presented in order of decreasing strength of association with the theme word. Presentation of the theme sets was separated by a 20-s interval during which subjects answered simple arithmetic problems (e.g., "2 plus 3").

After a 10-min break at the end of the study phase, the test phase was begun by instructing the subjects to lie on the flat scanner bed and asking them to make recognition judgments about words projected on the screen. The test words were presented in pairs from each theme set (Fig. 1). A total of 24 pairs of words extracted from each of 24 theme sets were equally assigned to one of the four conditions with a counterbalance across four versions of the test list: (i) old word–old word pair, consisting of the first and second strongest associates, (ii) old word–related lure pair, consisting of the theme word and the first strongest associate, (iii) related lure–related lure pair, consisting of the theme word and the third strongest associate, and (iv) unrelated lure–unrelated lure pair, consisting of the first and the second strongest associates. Therefore, none of the test words was presented more than once. The trials were pseudorandomly ordered so that there were never more than three trials of the same condition in a row. Subjects were instructed to respond with their left hand, pressing with their index finger to indicate "old "for both words in the pair, with their middle finger to indicate "old "for just the right word in the pair, with their ring finger to "old "for just the left word in the pair, and with their little finger to "new" for both words in the pair. They were also asked to respond while the words were being presented or after they were removed from the screen. The pair words were presented for 3 s and immediately followed by presentation of a cross-hair with stimulus-onset asynchronies (SOAs) of 30 s. Before starting the scanning session, the subjects briefly practiced pressing the buttons and understanding response mapping in order to minimize differences in reaction time between the different fingers and any impact of the difficult response mapping on the imaging results. All of the subjects completed the test within 20 min.

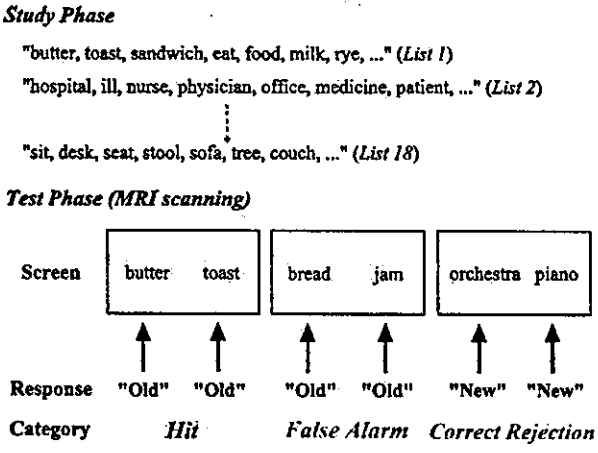


Fig. 1. Schematic diagram of the procedure. In the study phase, subjects were asked to try to remember 18 theme sets of 14 semantic associates outside the MRI scanner in preparation for a later recognition test in the scanner. In the test phase (MRI scanning session), subjects were asked to make recognition judgments with response buttons for word pairs presented on the screen, including old words, related lure (false) words, and unrelated new words. Among the various types of subjects' responses in all trials, imaging data for responses with hit, false alarm, and correct rejection for both of the word pairs were selected for the analyses.

*fMRI data acquisition*

A Siemens Magnetom VISION system on 1.5 T was used to acquire high-resolution T1-weighted anatomical images (1 mm isotropic voxel) and gradient-echo echo-planar T2*-weighted images with blood oxygenation level dependent (BOLD) contrast of 15 axial slices with 4 mm cubic resolution, a TE of 50.24 ms, and flip angle of 90°. Our slice selection focused mainly on the PFC (including the slices from $Z = -3$ to 33) so that the adjacent areas of hippocampus were outside the scanning field. A single volume consisted of 15 slices and each volume was acquired continuously every 2500 ms with an acquisition time of 1460 ms. Each behavioral trial corresponded to 12 volumes. A total of 24 trials per subject was collected in one run (732.5 s), yielding a total of 293 volumes. The first five volumes were discarded to allow for T1 equilibration effects. The scanner was synchronized with presentation of the stimuli.

*fMRI data analysis*

The data were analyzed by statistical parametric mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK: http://www.fil.ion.ucl.ac.uk/spm) (Friston et al., 1995b). The time series were realigned by rigid body transformation, corrected for movement-related effects by modeling geometric deformations (Andersson et al., 2001), and sinc interpolated in time to correct phase advance during volume acquisition (Aguirre et al., 1998). To enable inter-subject analyses, the images obtained were transformed to the Montreal Neurological Institute (MNI) standard space by using co-registered structural T1 scans with sub-sampling to an isotropic voxel size of 3 mm (Ashburner and Friston, 1999). We restricted the search volume for analysis to within the common area scanned across all subjects. The resulting images were smoothed in space with an isotropic 10 mm FWHM Gaussian kernel. In order to process the images with a time-course, they were high-pass filtered at 1/120 Hz and low-pass smoothed with a 4 s Gaussian filter (Henson, 2001). The BOLD response to the events of each response type (hit, false alarm, and correct rejection) was modeled with a Finite Impulse Response basis set of peristimulus time bins of 2.5 s duration that were equal to the scan repetition time. This general basis set captures any shape of the impulse

BOLD response up to the frequency limit imposed by the bin size and smoothing. These functions comprised the covariates in a fixed-effects general linear model (GLM) (Friston et al., 1995a; Worsley and Friston, 1995; Worsley et al., 1996) together with six movement parameters (the three translations and three rotations) analyzed from the realignment process in order to remove any residual movement-related artifacts. Contrasts were performed on the parameter estimates between bin 1 (the onset of stimulus presentation) and bins 2–4 (from 5.0–10.0 s post-stimulus presentation). They allowed a reasonable window during which the peak BOLD response including the late onset BOLD response was likely to have occurred. In this study, we used the model-free style of the BOLD as a method of analysis to detect activation areas with a long SOA of 30 s. The fMRI signal intensities obtained at the voxels in the whole image were compared by $t$ tests to determine whether a significant increase in signal had occurred since the onset of stimulus presentation. The resulting statistical maps were height-thresholded at $P < 0.001$ uncorrected for multiple comparisons. We determined activation areas to collect the highest $t$ value between bins 1 and 2–4 at each voxel for three types of responses (hit, false alarm, and correct rejection; see Results for details) and used the point of a local maximum voxel to create time-courses that indicate the relative fitted response changes from the onset of stimulus presentation.

The analysis of functional connectivity by the regression analysis (Büchel and Friston, 1998) treated the parameter estimates from the maximum voxel in each of the four PFC regions (bilateral anterior and posterior PFC) as the regressors in each design matrix, together with six movement parameters (the three translations and three rotations) analyzed in the realignment process, in order to remove any residual movement-related artifacts (see also methods in Lumer and Rees, 1999). The resulting parameter estimates at each voxel were compared by means of $F$ tests to determine whether significant functional connectivity had occurred. The statistical $F$ maps obtained were thresholded at $P < 1 \times 10^{-9}$ and corrected for multiple comparisons. The maxima of the activations were checked on normalized average images of EPI and T1 structural images.

## Results

### *Behavioral results*

Even though they recognized many of the old words as old and correctly rejected many of the unrelated new words as new, the subjects tended to recognize both of the related lure words as old. The results are based on what the subjects actually responded, not based on what they were expected to respond by an estimation from the properties of the study lists. Although we modified the DRM paradigm by using paired words to make the task more difficult and ensure activation in all four PFC regions, the analyses hereafter are based on three types of responses to prevent the results from becoming too complicated: *hit* is defined as a correct response for both old words in a pair, *false alarm* is defined as an incorrect response for both related lure words in a pair, and correct rejection is defined as a correct response for both unrelated new words in a pair. The mean number of responses of each type per subject was: 3.92 (SD = 1.33) for hit, 1.77 (SD = 0.80) for false alarm, and 4.23 (SD = 0.97) for correct rejection.

The mean proportion of correct responses for each type of response was 0.65 (SD = 0.22) for hit, 0.29 (SD = 0.13) for false alarm, and 0.72 (SD = 0.16) for correct rejection. A one-way ANOVA (type of response as a factor) yielded a significant main effect ($F(2, 24) = 24.05$, $P < 0.001$), and Ryan's post-hoc tests yielded significant differences between hit and false alarm ($t(2) = 5.46$, $P < 0.001$) and between false alarm and correct rejection ($t(2) = 6.44$, $P < 0.001$). The mean reaction time for each type of response was 2195 ms (SD = 1074 ms) for hit, 2164 ms (SD = 813 ms) for false alarm, and 3025 ms (SD = 1561 ms) for correct rejection. A Kruskal–Wallis test demonstrated a significant difference in reaction time between the three types of responses ($H(2) = 10.04$, $P < 0.01$). Mann–Whitney's post-hoc tests showed that the correct rejection responses were significantly slower than the hit and false alarm responses ($U = 755.00$, $Z = -3.03$, $P < 0.01$; $U = 329.50$, $Z = -1.96$, $P = 0.05$ respectively). Although the response latency of the different fingers did not differ in the practice session, it is reasonable to expect the little finger to tire more quickly during the correct rejection responses with an equivalent number of responses in the test phase.

### *Imaging results*

We first identified regions in the PFC that showed BOLD signal increases during responses for hit, false alarm, and correct rejection (Table 1). Significant activation areas for all response types were the bilateral posterior PFC (BA 9/44/45) and left frontal operculum (BA 47). In addition to these common areas, the bilateral anterior PFC areas (BA 10) showed significant BOLD signal increases during hit responses, whereas the right anterior PFC (BA 10) and right frontal operculum (BA 47) showed significant signal increases during false alarm responses. Significant signal increases for correct rejection responses were found in the left anterior PFC (BA 10) in addition to the common activation areas.

Table 1
Prefrontal regions showing significant BOLD signal increases during hit, false alarm, and correct rejection responses

| Region activation | Left/ right | Brodmann area | MNI coordinates | | | $t$ value |
|---|---|---|---|---|---|---|
| | | | $X$ | $Y$ | $Z$ | |
| *Hit (true recognition)* | | | | | | |
| Posterior prefrontal, GFm | L | 9/44/45 | −48 | 12 | 24 | 7.04 |
| Posterior prefrontal, GFm | R | 9/44/45 | 51 | 21 | 30 | 4.84 |
| Frontal operculum, GFi | L | 47 | −36 | 18 | −6 | 3.57 |
| Anterior prefrontal, GFm | R | 10 | 39 | 60 | 6 | 3.43 |
| Anterior prefrontal, GFm | L | 10 | −42 | 51 | 6 | 3.16 |
| *False alarm (false recognition)* | | | | | | |
| Posterior prefrontal, GFm | L | 9/44/45 | −39 | 21 | 15 | 4.57 |
| Posterior prefrontal, GFm | R | 9/44/45 | 51 | 12 | 30 | 4.52 |
| Frontal operculum, GFi | L | 47 | −36 | 21 | −3 | 3.70 |
| Anterior prefrontal, GFm | R | 10 | 30 | 60 | 18 | 3.36 |
| Frontal operculum, GFi | R | 47 | 45 | 18 | −6 | 3.13 |
| *Correct rejection* | | | | | | |
| Posterior prefrontal, GFm | L | 9/44/45 | −51 | 6 | 30 | 7.16 |
| Posterior prefrontal, GFm | R | 9/44/45 | 42 | 24 | 21 | 6.53 |
| Anterior prefrontal, GFm | L | 10 | −30 | 60 | 15 | 4.43 |
| Frontal operculum, GFi | L | 47 | −30 | 18 | 0 | 3.82 |

*Note.* GFm, middle frontal gyrus; GFi, inferior frontal gyrus.

*Time-course of activations in anterior and posterior PFC*

Time-course analyses of MR signals were conducted to examine the activation patterns in PFC regions. Percent signal change for hit, false alarm, and correct rejection in the four PFC regions were displayed based on the relative fitted responses obtained by the analysis for the local maximum voxel (left posterior: (−48, 12, 24), $t(1715) = 7.04$ for hit, (−39, 21, 15), $t(1715) = 4.57$ for false alarm, (−51, 6, 30), $t(1715) = 7.16$ for correct rejection; right posterior: (51, 21, 30), $t(1715) = 4.84$ for hit, (51, 12, 30), $t(1715) = 4.52$ for false alarm, (42, 24, 21), $t(1715) = 6.53$ for correct rejection; left anterior: (−42, 51, 6), $t(1715) = 3.16$ for hit and false alarm, (−30, 60, 15), $t(1715) = 4.43$ for correct rejection; right anterior: (39, 60, 6), $t(1715) = 3.43$ for hit, (30, 60, 18), $t(1715) = 3.36$ for false alarm and correct rejection).

Differential activation patterns were obtained in the four PFC regions for each type of response (Fig. 2). There were three prominent activation patterns: (i) the left anterior PFC (BA 10) showed a greater signal change for correct rejection (blue line) than for hit (red line) and false alarm (green line), (ii) the right anterior PFC (BA 10) showed a greater signal change for false alarm than for hit and correct rejection, and (iii) the left posterior PFC (BA 9/44/45) in the vicinity of the Broca's area was less activated for false alarm than for hit and correct rejection. The noteworthy findings were that the bilateral anterior PFC regions showed reversed activation patterns for false alarm (green line) and correct rejection (blue line) responses, indicating their independent episodic memory retrieval contributions and that the anterior and posterior PFC showed independent hemodynamic response patterns during episodic memory retrieval.

Since an important question concerning these findings was whether actual functional connectivity could be demonstrated between the right and left anterior PFC and between the anterior and posterior PFC regions, we used the functional connectivity method as a second-step analysis in an attempt to answer it.

*Functional connectivity in PFC*

The analysis of functional connectivity treated the parameter estimates from the maximum voxel in each of the four PFC regions (bilateral anterior and posterior PFC) as the regressors in each design matrix. Brain regions that exhibited increased functional connectivity over time that originated in the four PFC regions are indicated in Fig. 3.

An overall consistent finding was that the four PFC regions were connected to several other regions in addition to the PFC areas. The top two panels in Fig. 3 show the regions connected to the posterior PFC in each hemisphere. The bilateral posterior PFC is connected to a wide range of regions, including the contralateral posterior PFC, medial PFC, anterior and posterior cingulate cortex, precuneus, and other temporal, parietal, and occipital areas. The left posterior PFC (−48, 9, 27) is strongly connected to the right posterior PFC (51, 18, 30) ($F(1,2074) = 529.23$, $P < 0$), and the right posterior PFC (48, 18, 27) is strongly connected to the left posterior PFC (−45, 12, 24) ($F(1,2074) = 549.27$, $P < 0.001$.

The bottom two panels in Fig. 3 show the regions connected to the anterior PFC in each hemisphere. The anterior PFC regions on

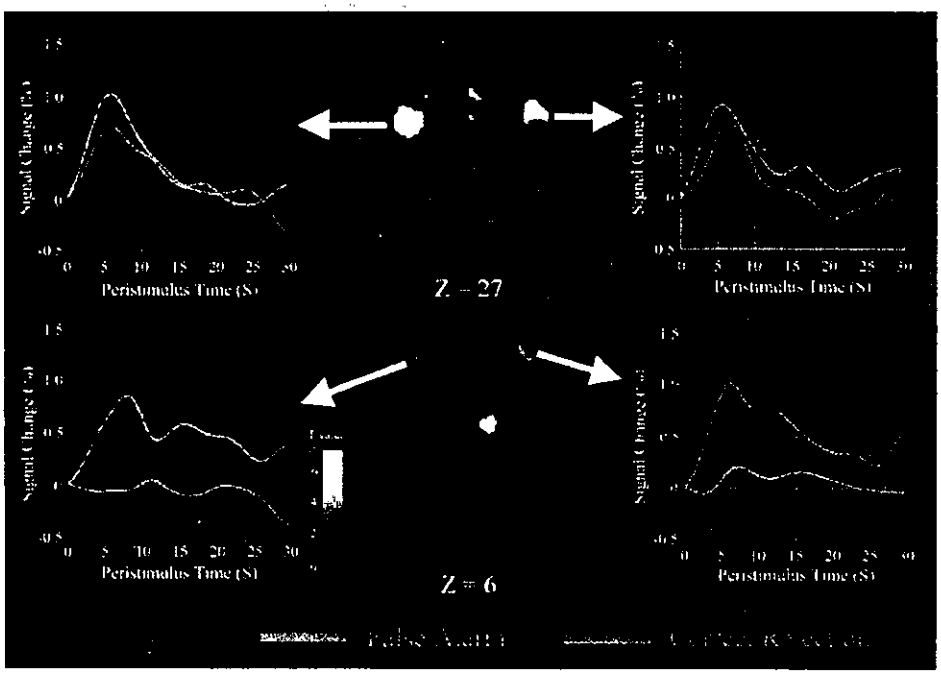


Fig. 2. Time-course of signal changes for hit, false alarm, and correct rejection in the four PFC regions. The regions were collected according to the highest $t$ value for each type of response. Time curves were drawn based on the relative fitted responses from the local maximum voxel obtained in the analysis. The top and bottom panels show activation patterns in the bilateral posterior and anterior PFC, respectively. These results indicate that the bilateral anterior PFC showed reversed activation patterns for false alarm and correct rejection responses and that anterior and posterior PFC showed independent hemodynamic response patterns during episodic memory retrieval.

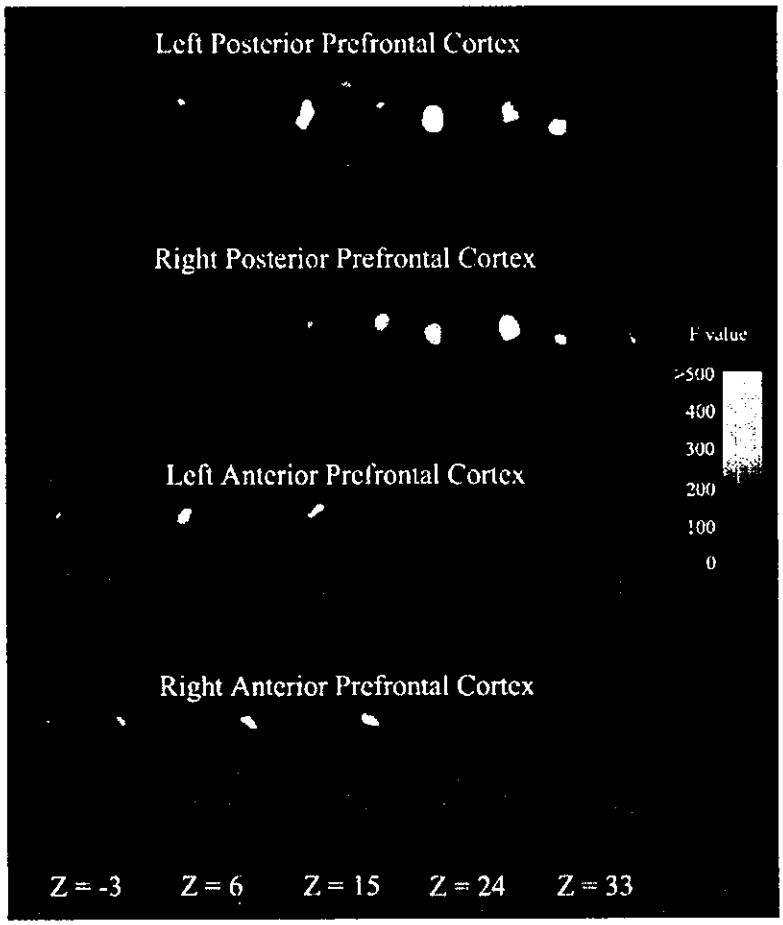


Fig. 3. Functional connectivity showing regional interactions in the PFC network. The analyses treated the parameter estimates from the maximum voxel of each of four PFC regions as the regressors in each design matrix (left posterior PFC: (−48, 12, 24) for hit, (−39, 21, 15) for false alarm, (−51, 6, 30) for correct rejection; right posterior PFC: (51, 21, 30) for hit, (51, 12, 30) for false alarm, (42, 24, 21) for correct rejection; left anterior PFC: (−42, 51, 6) for hit and false alarm, (−30, 60, 15) for correct rejection; right anterior PFC: (39, 60, 6) for hit, (30, 60, 18) for false alarm and correct rejection). Areas that exhibited increased functional connectivity over time as the origin of the four PFC regions were drawn on each panel. The top two panels of the figure represent the regions. Functional network in the prefrontal cortex during episodic memory retrieval connected to posterior PFC in each hemisphere. The left posterior PFC (−48, 9, 27) was strongly connected to the right posterior PFC (51, 18, 30), and the right posterior PFC (48, 18, 27) was strongly connected to the left posterior PFC (−45, 12, 24). The bottom two panels of the figure represent the regions connected to the anterior PFC in each hemisphere. Contrary to the findings in the posterior PFC, the left anterior PFC (−30, 60, 15) was more weakly connected to the right anterior PFC (42, 57, 9) than the posterior PFC regions of each hemisphere were to each other, and the right anterior PFC (30, 60, 18) was weakly connected to the left anterior PFC (−39, 51, 18). These findings provide concrete evidence in support of the hypothesis that the anterior and posterior PFC make differential contributions during episodic memory retrieval.

both sides is connected to a smaller range of regions than the posterior PFC. More importantly, the left anterior PFC (−30, 60, 15) is more weakly connected to the right anterior PFC (42, 57, 9) ($F(1,2074) = 206.57$, $P < 0.001$) than the posterior PFC regions is to each other, and also the right anterior PFC (30, 60, 18) is weakly connected with the left anterior PFC (−39, 51, 18) ($F(1,2074) = 168.79$, $P < 0.001$).

In summary, there were two substantial findings in regard to the PFC network. First, the posterior PFC in each hemisphere has strong functional interconnections with the contralateral posterior PFC, whereas the anterior PFC in each hemisphere has only weak functional interconnections with the contralateral anterior PFC. Second, no strong functional interconnection was found between the anterior and posterior PFC in either hemisphere. These findings provide concrete evidence that supports the hypothesis that the anterior and posterior PFC make differential contributions to episodic memory retrieval.

## Discussion

The main goal of the present study was to identify the interrelation between brain activity in the right and left PFC during episodic memory retrieval. The data obtained by fMRI and the functional connectivity analysis revealed strong functional interconnections between the posterior PFC on each side and the contralateral posterior PFC but only weak functional interconnections between the anterior PFC and the contralateral anterior PFC. The results also indicated the absence of strong functional interconnections between the anterior and posterior PFC in each hemisphere. Our findings in this study provide strong evidence for the hypothesis of associative contributions of the bilateral posterior PFC and dissociative contributions of the bilateral anterior PFC to episodic memory retrieval. One explanation for the strong functional interconnections between the bilateral posterior PFC is that it

is a result of cognitive compensation by the two areas. In view of the difficulty of our task, dividing cognitive processing across the hemispheres may be more efficient because it allows for parallel processing (Banich, 1998). As Reuter-Lorenz (2002) stated in the compensatory-recruitment hypothesis, additional recruitment evident in older brains resembles the response of younger brains to increased task difficulty. The strong functional interconnections between the bilateral posterior PFC may be a result of mutual compensatory processing by the areas to enable optimal performance. Our findings may be direct evidence of the pattern of the prefrontal functional linkage during episodic memory retrieval. Furthermore, the results of our time-course analyses revealed reversed activation patterns in the bilateral anterior PFC between false alarm and correct rejection responses, whereas the bilateral posterior PFC showed similar patterns of activation. These findings suggest that the anterior PFC on each side plays a different role during episodic memory retrieval, whereas the posterior PFC is concerned with equivalent processing bilaterally. Our data also support differential contributions of the anterior and posterior PFC during episodic memory retrieval.

We used the functional connectivity method to examine the interactions among the PFC areas in this study. Functional connectivity is defined as the temporal correlation between spatially remote neurophysiological events and is simply a statement about the correlations observed (Friston et al., 1993a). There is another connectivity method, the effective connectivity, which is defined as the influence that one neural system exerts over another either directly or indirectly (Friston et al., 1993b). In view of the limitation of using effective connectivity to infer causality based on temporal precedence due to different response latencies, we selected functional connectivity to identify connectivity patterns among different regions in this study (Horwitz, 2003; Lee et al., 2003). We therefore used the complete time series data of fMRI signal intensities in the brain regions to account for our data, and as a result, our functional connectivity data may not reflect momentary cognitive activity. Further study is required to address these limitations.

Another question concerns the areas analyzed in the functional connectivity analysis. Our analyses in the present study were focused on the functional network in the PFC, but areas outside PFC, such as the hippocampus, are also crucial for comprehensive understanding of episodic memory retrieval. In fact, Maguire et al. (2000) observed increased connectivity between the parahippocampal cortex and hippocampus during retrieval of autobiographical events and increased connectivity between the middle temporal gyrus and temporal pole during retrieval of general knowledge. In support of their findings, Maguire et al. (2001) also obtained neuropsychological data showing no apparent increase in connectivity between the parahippocampal cortex and hippocampus in a patient with selective bilateral hippocampal pathology (Maguire et al., 2001). Although further studies are needed to integrate our understanding of functional connectivity, our data obtained in the present study should make a considerable contribution to achieving that goal.

One of the other noteworthy findings in the present study is that the right anterior PFC showed a greater signal change for false alarm than for hit and correct rejection. Although the results of previous neuroimaging studies are complicated in regard to which regions are more involved during false alarm responses, our results are consistent with the recent finding of greater activation of the right PFC during false alarm (Cabeza et al., 2001; Schacter and Slotnick, 2004; Slotnick and Schacter, 2004). Our data are also supported by neuropsychological findings (Schacter et al., 1996c). One possible explanation for the finding of greater activation of the PFC during false alarm is that the right anterior PFC is sensitive to familiarity based on the semantic contexts created by the word lists presented in the study phase, and this explanation is consistent with the previous arguments suggesting that the right PFC subserves familiarity or recency judgments (Johnson and Raye, 1998; Ranganath et al., 2000). Because of the longer delays between the study and the test phase in our present study and the fact that the test items were presented in pairs, the results include evaluational processes in addition to retrieval processes. Previous neuroimaging studies that examined the neural correlates of evaluation by minimizing retrieval processes have shown that the right PFC is recruited during evaluation of recency or familiarity (Johnson et al., 2003; Mitchell et al., 2004). Our finding that the signal increase in the right anterior PFC was greater for false alarm responses led us to speculate that the excessively high sensitivity to familiarity in the right anterior PFC may be a cause of the frequent occurrence of false alarm responses (Schacter et al., 1996c). Another possible explanation is that the greater signal change in the right anterior PFC reflects greater monitoring load (Allan et al., 2000; Henson, 2000; Henson et al., 1999b; MacLeod et al., 1998; Rugg et al., 1999; Schacter et al., 1997). The greater signal change in the right anterior PFC for false alarm may be explained by deep involvement in monitoring when false alarm responses occurred.

Some recent findings have suggested that the left anterior PFC subserves source monitoring, evaluations of specific memory characteristics, and accurate episodic retrieval (Cansino et al., 2002; Henson et al., 1999a; Johnson and Raye, 1998; Ranganath et al., 2000). These systematic retrieval processes appear to be required for correct rejection rather than for hit and false alarm because retrieval load, which may be determined by the inverse of the levels of familiarity, would be greater for correct rejection responses. The finding of a greater signal change in the left anterior PFC for correct rejection than for hit and false alarm suggests a major contribution of the left anterior PFC to systematic source monitoring or conscious recollection. Indeed, the mean reaction time for correct rejection responses was significantly slower than for hit and false alarm. Taking into account the relatively late responses by the little finger, the response delay of more than 800 ms suggests a higher load for correct rejection responses. These findings are also supported by our functional connectivity findings showing that the anterior PFC on each side has relatively independent functional connectivity, and they seem to support the hypothesis that, when the familiarity-based processing in the right anterior PFC is high, the recollection-based processing in the left anterior PFC is low, and vice versa.

In contrast to the differential contributions of the bilateral anterior PFC to episodic memory retrieval, the time-course of bilateral posterior PFC activity showed no substantial difference among the three types of responses except for smaller activation for false alarm in the left posterior PFC (in the vicinity of the Broca's areas). These results indicate the absence of any strong connection between the anterior and posterior PFC in this study, which supports the hypothesis that the anterior and posterior PFC have differential roles during episodic memory retrieval. The finding of smaller activation in the left posterior PFC during false alarm responses suggests that insufficient verbal processing may be another cause of the occurrence of false alarm responses.

Previous functional imaging studies of the neural mechanism of false recognition have demonstrated late onset of anterior PFC

during recognition judgments (Schacter et al., 1997) and that activity in the posterior medial temporal lobe regions distinguishes responses for true from false items (Cabeza et al., 2001). Although these findings provide some support for our understanding of the mechanisms of false recognition, they were insufficient because the data were based on all responses for related lure words, and thus they included actual false alarm and correct rejection responses (Cabeza et al., 2001; Schacter et al., 1997). In this study, we treated only actual false alarm responses for both of the pair words. Thus, the present findings using stricter criteria are even more helpful in understanding the neural base of false recognition.

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Note

# A 3-year follow-up study of 'orientation agnosia'

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**Abstract**

Dissociation between the ability to recognize misoriented objects and to determine their orientation has been reported in a small number of patients, but the long-term course of this deficit has not been reported so far. Here, we describe the case of a 32-year-old female who had bilateral occipito-temporal damage caused by a cerebrovascular accident. Neuropsychological assessment performed at 6 months after the occurrence of the cerebrovascular accident revealed that she was almost generally agnostic for object orientation. The patient was then re-tested 3 years later, when she showed apparently striking recovery in her ability to determine object orientation. However, closer examination revealed that she still displayed the same impairment, although at this time, it was only for objects presented in non-cardinal angles. Moreover, she had problems mostly discriminating orientations that differed by small amounts. The ability of patients to discriminate a variety of orientations should be further tested in future investigations in this field.


*Keywords:* Visual recognition; Brain damage; Human

## 1. Introduction

It has been reported that certain patients with some neurological disorders are able to achieve object recognition while lacking knowledge of the orientation of the object, which means that the ability to judge the spatial attributes of an object, including the orientation, is dissociated from the ability to recognize and name the object. Turnbull et al. have offered the most detailed account of this phenomenon, which they term "agnosia for object orientation". They have described three cases in which a clear dissociation was noted between a preserved ability to identify objects presented in different orientations and the ability to correctly recognize the presented orientation of the object (Turnbull, Beschin, & Della Sala, 1997; Turnbull, Laws, & McCarthy, 1995). The disorder is especially intriguing with regard to object recognition from multiple viewpoints, which has been a matter of long debate in experimental psychology as well as computational vision science (Deneve & Pouget, 2003; Riesenhuber & Poggio, 2000). It is a remarkable feature of our visual system that it allows us to recognize objects, regardless of the viewpoints they are seen from. The basis for this ability is a subject of much controversy in the visual recognition literature. One proposal is that the representation of objects in the long-term memory codes features in a manner that is independent of the object orientation. According to this theory, incoming stimuli are similarly described using representations that do not encode the viewpoints, and are therefore termed "viewpoint-independent" (Corballis, 1988; Marr & Nishihara, 1978). On the other hand, a "viewpoint-dependent" theory has been put forth, which hypothesizes that objects are represented in long-term memory in typical orientations, and misoriented stimuli are aligned by a process of analogue imagery transformation (such as mental rotation) (De Caro, 1998; Jolicoeur, 1988; Tarr & Pinker, 1989). Turnbull and colleagues speculated that the orientation agnosia in their cases reflects the existence of an orientation-independent (viewpoint-independent) route to object recognition, thus lending support to the viewpoint-independent theory of object recognition.

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Karnath, Ferber, & Bulthoff (2000), however, argued against this viewpoint-independent hypothesis based on the observations in their patient KB, who made no errors in her orientation judgement when the items were upright, but whose response accuracy dropped to chance levels when the items were presented in non-upright orientations. The authors concluded that this visual recognition disorder was caused by the failure of a neural system that codes orientation information. They contended that upright orientations, by virtue of their stronger representation, were more robust against neuronal damage. Based on such evidence, Karnath et al. suggested that these patients do not have an "agnosia for object orientation", but rather "a disability in determining the orientation predominantly of those objects that had a non-upright orientation". They further refuted, based on the same consideration, the claim that the findings in the patients can be interpreted as suggesting that object structure is coded in an orientation-invariant (viewpoint-independent) way.

In turn, Turnbull, Della Sala, & Beschin (2002) argued against the above contention of Karnath et al. by reporting the finding that in reaction time tasks using rotated objects, patients recognized items at 0° no faster than rotated items and made as many errors in recognizing objects at 0° as they did in recognizing those rotated at 120°. They argued, therefore, that their patients' disorder did indeed represent 'orientation agnosia', and supported the claim that objects are typically recognized using a mechanism that is viewpoint-independent. On the other hand, in a study on Alzheimer's disease patients, Turnbull et al. demonstrated that recognition errors were greater for objects that were rotated than for those that were at 0°, and acknowledged mixed support for Karnath et al.'s theory (Caterini, Della Sala, Spinnler, Stangalino, & Turnbull, 2002).

More recently, an alternative view was put forward by Harris et al., which they call "a failure to find the axis". In their report, patient EL, a case of probable Alzheimer's disease, displayed a profound inability to judge the orientation of non-upright objects, but remarkably retained intact knowledge of the upright orientation. Strikingly, his orientation judgement was also more accurate for upside-down objects (i.e., 180°) than for other orientations (Harris, Harris, & Caine, 2001). Harris et al. interpreted these results as evidence that judgement of object orientation is facilitated when the orientation of the principal axis of the object matches that of an internal representation. Thus, they propose that this disorder is related to a failure to locate an object's principal axis.

In this paper, we report a new patient who showed apparent dissociation between a knowledge of object identity and that of object orientation after suffering a cerebrovascular accident. The availability of neuropsychological data from this patient 3 years after the occurrence of the cerebrovascular accident draws special interest in this case. While the data initially suggested striking recovery from the earlier deficit, more detailed testing revealed that the patient still exhibited some residual deficit related to orientation judgement.

## 2. Case report

RU was a 32-year-old right-handed female patient who was found to have multiple brain infarctions when she recovered from consciousness disturbance caused by antihypertensive drug overdose. She was admitted to the neurological unit with right hemiparesis, right spatial neglect and alexia. MRI revealed bilateral lesions in the occipito-parietal cortex (Fig. 1). After 2-months' conservative treatment, when she recovered from the aforementioned neurological deficits, the patient was admitted to a rehabilitation center. While an inpatient at the rehabilitation center from December 2000 to February 2001, she was assessed on a subset of the WAIS-R and scored a verbal IQ of 77. However, she was unable to complete any items on the Performance Scale due to severe perceptual and spatial difficulties. In view of this poor performance, her perceptual ability was investigated in greater detail and she was found to have associative visual agnosia at 3 months after the occurrence of the cerebrovascular accident (she had difficulty recognizing a variety of visually presented objects and drawings, but could successfully match pairs of visual stimuli as being the same or different). While she had almost recovered from this deficit at 6 months after the occurrence of the cerebrovascular accident, it was found that she still could not judge line orientation correctly. In addition, impairment of object orientation recognition was also seen in daily life, e.g., she could not read the time from the positions of the hands on a clock.

In order to further investigate and quantify this deficit in our patient, we conducted a series of experiments to test her ability to detect object at two time-points, namely at 6 months and at 3 years after the onset. Three healthy subjects (two females and one male; mean age $33.3 \pm 1.2$) also participated as normal subjects, obtaining an accuracy of 100% in each task unless stated otherwise.

### *2.1. Investigation at 6 months after the onset*

Because the clinical impression was of 'orientation agnosia', a series of tasks to confirm this condition according to the protocols in previously published literature were given to RU. Line drawings used for the experiments were selected from the Snodgrass and Vanderwart corpus (Snodgrass & Vanderwart, 1980). The drawings were selected so that they represented objects in unambiguous canonical upright orientations.

#### *2.1.1. Task 1: Object recognition versus knowledge of the object's canonical orientation*

In this experiment, RU's ability at object recognition was compared with her knowledge of the same object's canonical orientation. Thirty-five pictures of objects were presented individually on a total of four occasions, each time in one of the four different cardinal orientations (0°, 90°, 180°, 270°). RU was first required to name the item as it was presented, and then to judge the correct orientation of the object.

Fig. 1. MRI scan 2 months post onset (left brain on right side). Bilateral lesions visualized in the occipito-parietal cortex.

RU correctly named all the 35/35 items with ease. In contrast to her excellent recognition of the objects that were presented in different orientations, RU showed profound impairment in her ability to judge the object's orientation; she could correctly judge the orientation of only 5/35 items. In fact, she got all the upright objects correct; she said that they all looked upright. These results suggested that RU exhibited distinct dissociation between her ability at object recognition and her ability to correctly judge the same object's canonical orientation.

*2.1.2. Task 2: Knowledge of the object's canonical orientation*

Pictures of 35 objects, each printed on a separate card, were prepared. RU was asked to rotate the cards so as to bring the pictures of the objects to their canonical upright position. She was instructed to indicate to the examiner when the 'upright orientation' of the object was reached (Karnath et al., 2000).

RU correctly performed the task for only 5/35 items. The task was essentially the same as that presented by Karnath et al. to their patient KB, who successfully performed this task with ease. Based on the performance of their patient, Karnath et al. argued that the disorder did not represent "agnosia for object orientation", but rather "a disability to determine the orientation predominantly of those objects that have a non-upright orientation". In contrast, RU in our study showed severe deficit in correctly determining even the upright orientation of the stimuli. Thus, RU seemed to have a poor knowledge of the canonical upright orientation of the objects presented to her.

*2.1.3. Task 3: Orientation discrimination (matching)*

Four copies of each selected drawing were printed in four different orientations (0°, 90°, 180°, 270°) on a square card. RU's task was to match the sample stimulus with the figure of the same orientation on the square card.

RU could not match any of the drawings (0/6). Because she did not have simultanagnosia, her performance indicated that RU had severe difficulty in matching the orientations of the objects.

*2.1.4. Task 4: Copying misoriented drawings*

The same drawings as those used in Task 3 were used. The stimuli were rotated to 0°, 90°, 180° and 270°, and reproduced on square cards. The drawings of the objects in each of the four different cardinal orientations were presented to RU, who was required to copy the objects at the presented orientation.

RU copied all of the forms with reasonable accuracy, but copied the rotation of 7/10 items incorrectly. She drew all 10 objects in their canonical upright position. The result implied that RU had some knowledge of the canonical upright orientation of the objects.

*2.2. Investigations at 3 years after the onset*

Tasks 1–3 described below were essentially the same as those given to the patient at 6 months, except for Task 3, in which orientation discrimination was tested in greater detail.

*2.2.1. Task 1: Object recognition versus knowledge of the object's canonical orientation*

This task was identical to Task 1 presented to the patient at 6 months after the occurrence of the cerebrovascular accident.

RU correctly named, as well as judged the orientation, of all the 35/35 items with ease. Thus, she performed with maximum accuracy, giving 100% correct responses.

*2.2.2. Task 2: Knowledge of the object's canonical orientation*

This task was also identical to Task 2 presented to the patient at 6 months.

RU performed correctly in 100% of the items. Together with the results in Task 1, one can reasonably conclude that

at this time-point, RU had perfect knowledge of the object's canonical orientation.

*2.2.3. Task 3: Orientation discrimination (matching) (cardinal or non-cardinal orientations)*

RU was presented with pairs of identical objects and was asked to determine whether they were in the same or in different orientations. Tasks 3a–3c (20 trials each) tested her ability at discrimination of unambiguous cardinal orientations (3a, 0° versus 180°; 3b, 0° versus 90°; 3c, 90° versus 270°), while Task 3d, consisting of 30 trials, tested her ability to discriminate non-cardinal orientations (discrepancies in the orientations of two objects positioned at various angles between 20° and 170°).

RU's performance was strikingly different across orientations. In Tasks 3a–3c, RU was easily able to discriminate the orientations of the two objects. In contrast, in Task 3d, her performance was worse than that in Tasks 3a–3c (23/30, 77% correct; controls performed 97.7% correct). Six out of the seven incorrect responses in Task 3d were for pairs whose discrepancies in orientation were less than 90°. These results showed that RU could successfully discriminate between two misoriented items only when the items were presented at cardinal (0°, 90°, 180°, 270°) orientations.

## 3. Discussion

RU, who had bilateral occipito-parietal damage after a cerebrovascular accident, showed normal object recognition but an impaired ability to judge object orientation. This disorder became evident at 6 months after the occurrence of the cerebrovascular accident, when her ability to establish the canonical upright orientations of individual objects (Tasks 1 and 2), to match the cardinal orientations of object drawings (Task 3), and to copy rotated drawings (Task 4) was investigated. Her performance was not consistent with the performance of Karnath's case, KB, who had perfectly preserved knowledge of the upright orientation, but was more similar to that of Turnbull et al.'s three key cases, who were labeled as having 'orientation agnosia'. However, that RU could draw objects in their upright canonical orientation suggested that she had some knowledge of the upright orientation. Thus, at this stage, our results led us, as also conceded by Turnbull et al. to offer mixed support for Karnath et al.'s hypothesis. Our observations at 6 months therefore just placed on record another case with so-called 'orientation agnosia'.

Because all of the earlier descriptions of related cases reported so far have been based on relatively short-term observations, the availability of neuropsychological data from our patient 3 years after the onset made her a case of special interest. Our patient showed a striking recovery of her ability for orientation judgement; that is, in the conventional orientation judgment tasks (Tasks 1–3c), RU performed with maximum accuracy, giving 100% correct responses.

However, closer investigation revealed that she still had some impairment of orientation judgement, i.e., in the matching task (Task 3), although she was able to determine object orientation perfectly when the item was presented at cardinal angles (0°, 90°, 180°, 270°), her judgement accuracy dropped strikingly when the items were rotated in non-cardinal angles. Moreover, she had problems mostly discriminating orientations that differed by small amounts (lees than 90°, Task 3d), which suggested that her residual deficits only really apply to these finer discriminations. Therefore, even by 3 years after the onset, RU's ability for orientation judgement had not fully recovered. In none of the previous studies were such detailed tests performed over the long-term, hence it remains unclear whether the other reported cases also had the same type of impairment as that exhibited by our case.

The fundamental impairment underlying the dissociation between the ability to recognize misoriented objects and the ability to determine their orientation seen in certain neurological patients has still not been elucidated, owing, at least in part, to the heterogeneity of performance of different reported cases: each case's ability to determine object orientation differed depending on the presented orientation of the stimulus (Harris et al., 2001; Karnath et al., 2000; Turnbull et al., 1995, 1997). While the differences may reflect the distinctiveness of each case, they may also be a reflection of the severity of each case, or the stage of the disorder, i.e., the 'orientation agnosia' described by Turnbull et al. may represent the most severe form, and the deficit described by Harris et al. in EL may represent the least severe form. The observations in our case, RU, seem to support this latter view: her performance at 6 months after the onset was similar to that of the patients with the most severe deficit as described by Turnbull et al., and that at 3 years after the onset, the deficit was milder than the deficit described by Harris et al. in their patient.

This statement is a mere speculation based on RU's performance and those of other previously reported cases. Therefore, the propositions made here await further confirmation from future research. RU is the only case so far in whom recovery over the long-term has been observed. Moreover, our testing was limited, i.e., not fully structured, due to clinical considerations, and the process of recovery could not be investigated. However, given the rarity of the disorder and the significance of the object recognition theory, we believe that the present speculation merits attention.

As for the anatomical basis, the disorder has been investigated in the context of the 'two cortical visual systems' approach, that postulates the separation of the processes of object recognition from those involved in certain types of spatial coding: one route (the dorsal system) is dedicated to the control of actions and codes a viewer-centered representation. The other route (the ventral system) is concerned with object recognition and codes an object-centered representation (Goodale & Milner, 1992; Mishkin, Ungerleider, Macko, 1983). On this account, the proposition of 'orientation agnosia' would be consistent with the existence of the object-centered perceptual system, in the

absence of the viewer-centered system. This profile provides tentative support for the distinction between a ventral route to object recognition which is not orientation-dependent, but which probably also codes for the usual upright orientation of objects, and a more dorsally located neural mechanism for processing the orientation of objects for other purposes. Indeed, Turnbull et al. (1995) interpreted the observation of dissociation between normal object recognition and an impaired sense of object orientation as being mediated via the viewpoint-independent ventral stream in the absence of the dorsal stream that carries orientation information.

However, recent developments in vision science suggest that there is a continuum from viewpoint-independence to viewpoint-dependency, which is in part influenced by stimulus discriminability and the task at hand (Bar, 2001; Biederman & Bar, 1999; Edelman, 1995; Hayward & Tarr, 1997; Vanrie, Beatse, Wagemans, Sunaert, & Van Hecke, 2002). The debate around 'orientation agnosia' would certainly be more fruitful when it is discussed taking into consideration this continuum theory.

The present case, RU, exhibited so-called "orientation agnosia" 6 months after cerebrovascular accident; at face value this seemed to support the viewpoint-independent theory of visual recognition. At 3 years after the cerebrovascular accident, however, her orientation judgement was intact for cardinal orientation but disturbed for non-cardinal orientations, which could be interpreted as indicating that at least some viewpoint dependency existed in her ability to perceive object orientation, consistent with the continuum hypothesis.

We propose that to elucidate the basis of this rare disorder in some neurological patients who show an apparent dissociation between their knowledge of object identity and that of object orientation, experiments examining the patients' ability to judge a variety of non-cardinal orientations should be planned and conducted in the future.

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# 和　文

# 脳イメージングによる抗精神病薬の薬効評価

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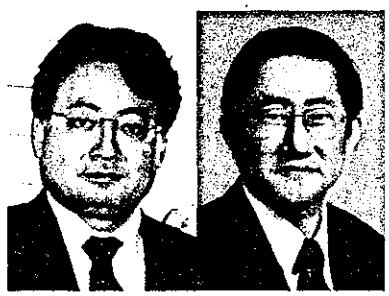

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## 1—はじめに

統合失調症の治療に使われる抗精神病薬は中枢神経の神経伝達機能に作用する。Positron Emission Tomography（PET）は放射性同位元素で標識した化合物（トレーサ）を生体に投与し、その経時的動態や分布を体外計測することが出来る核医学的検査法である。標識する化合物の選択によって脳内情報伝達系の多様な機能を測定することが可能なことから、抗精神病薬の脳内作用を評価に利用され成果をあげつつある。

PETを用いて抗精神病薬の脳内作用の評価法としては、生体内で受容体に結合する薬剤がどの程度受容体に結合しているかトレーサの特異結合の減少度を占有率として評価する方法が用いられている。このような方法を用いて、抗精神病作用や錐体外路性副作用（EPS）の発現機序を理解しようとする試みが進みつつある。

## 2—線条体D2受容体占有率

Fardeらは、benzamide系の抗精神病薬であるraclopride を[$^{11}$C]で標識してPETトレーサとして用い、抗精神病薬あるいは三環系抗うつ薬により治療中の患者の線条体D2受容体を調べた[1]。その結果、抗精神病薬では65%～85%の線条体D2受容体が占有されていることを見出した。この所見は、治療量の抗精神病薬が確かにD2受容体遮断作用を発揮しているということを確認した重要な所見である。さらに、Fardeら[2]がhaloperidolなどの定型抗精神病薬により治療中の22例の患者で調べたところ、70～89%の線条体D2受容体占有率が認められた。以上の結果から、抗精神病作用が発揮されるためには、おおよそ70%以上という、D2受容体占有率における治療閾値の存在が示唆された。さらに抗精神病薬服用中の患者でEPSを認めた群では線条体D2受容体占有率が80%以上でより高かったという。

このように抗精神病作用をもたらす受容体占有率（治療閾値）よりも錐体外路症状をもたらす受容体占有率（副作用閾値）の方が高いことから、治療閾値と副作用閾値の間、すなわち70から80%にD2受容体占有率を設定することによって、副作用を回避しつつ抗精神病作用を期待できる合理的な用量設定が可能になると考えられる（図1）。

さて、clozapineは、臨床的には明確な抗精神病作用を示しながら、EPSをほとんど認めないこと、行動薬理学的にもカタレプシー作用を欠いていることから、既存の定型抗精神病薬に対して非定型抗精神病薬と呼ばれる。治療量の定型抗精神病薬が70%以上のD2受容体占有率を示すのに対して、clozapineは用量を増やしても70%以上のD2受容体占有率に達しないことが明らかにされており、clozapineがEPSを引き起こしにくいことをよく説明していると考えられている[2]。

## 3—5-HT$_2$受容体占有率

Nordstromら[3]は、clozapineの血中濃度と5-HT$_2$受容体占有の関連を調べ、線条体D2受容体の占有率が治療閾値70%を越えないのに、5-HT$_2$受容体占有率は80%以上と高いことを報告した。このようなclozapineの持つ5-HT$_2$受容体遮断作用は、新世代の抗精神病薬の開発に大きな影響を与えてきた。近年、開発導入された抗精神病薬の多くは、D2受容体遮断作用に加えて、強力な5-HT$_2$受容体遮断作用を持っている。最近わが国で、臨床導入されたrisperidone、olanzapine、quetiapineについてはどちらも、D2受容体占有率に比べて、5-HT$_2$受容体占有率が高いことが指摘されている[4]。このような所見は動物を用いた*in vitro*の受容体実験で示されている非定型抗精神病薬の「5-HT$_2$作用＞抗D2作用」の特徴とも一致している。

## 4—辺縁系選択性

脳内のドーパミン神経回路には、黒質緻密部を起始核として線条体へ投射する黒質線条体系の他に、中脳腹側被蓋野を起始核として、辺縁系や前頭葉に投射する中脳辺縁系や中脳皮質系がある。この内、黒質線条体系は、運動機能に関連していることから、抗精神病薬による線条体D2受容体の占有率がEPSと相関するの